

Apixaban for Routine Management of upper extremity Deep Venous Thrombosis

(ARM-DVT)

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SUMMARY:

Background: Upper extremity deep vein thrombosis (UEDVT) constitutes approximately 10% of all DVT. A recent increase in incidence is largely secondary to the increasing use of peripherally inserted central venous catheters. Treatment for UEDVT is derived from evidence for treatment of lower extremity deep vein thrombosis (LEDVT). No evidence exists for the use of a direct oral anticoagulant (DOAC) for the treatment of UEDVT.

Population: Sequential patients identified within the Intermountain Healthcare system and University of Utah Healthcare system with UEDVT defined as the formation of thrombus within the internal jugular, subclavian, axillary, and brachial veins of the arm demonstrated by imaging.

Intervention: Apixaban 10 mg PO twice daily for 7 days followed by apixaban 5 mg twice daily for 11 weeks.

Comparison: In our primary analysis we will report the rate of clinically overt objective VTE and VTE-related death in comparison to the rate reported upon literature review ("reference value in the literature"). If the confidence interval for this rate excludes the commonly accepted threshold event rate of 4%, we will conclude that treatment with apixaban is noninferior, and therefore a clinically valid approach to treat UEDVT. As a secondary analysis we will compare the rate of the primary efficacy outcome and primary safety outcome with a historical control of case matched patients with UEDVT ("historical control") treated with therapy conventional (low molecular weight heparin plus warfarin) prior to the approval of DOACs.

Sample Size: A sample size of 357 patients who meet eligibility criteria was chosen so that an exact 95% confidence interval would exclude an event rate of venous thromboembolism (VTE) in the observation cohort of 4%. We will add 5% for anticipated withdrawal to assure adequate patient enrollment in the case of patient withdrawal and enroll 375 patients.

Outcome: 90 day rate of new or recurrent objectively confirmed symptomatic venous thrombosis and VTE-related death. The primary safety outcome is major bleeding and clinically relevant nonmajor bleeding.

1.0 GENERAL OBJECTIVE:

To assess the safety and effectiveness of apixaban for the treatment of upper extremity deep vein thrombosis (UEDVT) and major and clinically important bleeding.

2.0 OUTCOMES:

2.1 Primary efficacy outcome:

90-day rate of recurrent symptomatic venous thrombosis and venous thromboembolism-related death (defined in section 11). If the event rate we observe for venous thromboembolism (VTE) excludes 4% derived from the reference value in the literature, we will assume noninferiority. As a secondary outcome the event rate we observe will be compared with the historical control.

2.2 Primary safety outcome:

90-day rate of major and clinically relevant nonmajor bleeding (defined in section 11). If the upper bound of the 95% confidence interval for event rate for the composite outcome of major bleeding and clinically relevant nonmajor bleeding excludes 13% we will consider apixaban as noninferior to warfarin.

2.3 Secondary outcomes:

Patient satisfaction with anticoagulation based on a standardized questionnaire,¹ post-thrombotic syndrome quality of life will be assessed using standardized assessment tool,² thrombosis-specific quality of life based on a standardized assessment.³ These outcomes will not be compared with any historical control or case matched patients or reference value in literature. We will analyze the composite outcome of VTE (efficacy) and bleeding (safety) in a similar manner as noted for the primary efficacy and safety outcomes.

2.4 Exploratory Outcomes:

We will report separately the 90-day rate of recurrent symptomatic venous thrombosis and venous thromboembolism-related death among patients with cancer-associated thrombosis (CAT). We will report separately the rate of 90-day major bleeding and clinically relevant nonmajor bleeding among patients with CAT.

3.0 BACKGROUND AND RATIONALE:

UEDVT refers to the formation of fibrin clots within the subclavian, axillary, and brachial veins of the arm.⁴ UEDVT may be either primary (without apparent inciting factor) or secondary (often in conjunction with a central venous catheter--CVC; malignancy, pregnancy, surgery, or trauma). UEDVT constitutes approximately 10% of all deep vein thrombosis (DVT),⁵ with an overall increase in incidence largely secondary to the increasing use of peripherally inserted central venous catheters (PICCs) for both inpatient and outpatient care. Indeed, approximately 50% of all UEDVT is attributed to CVCs⁶⁻⁸ with a contemporary overall incidence of symptomatic UEDVT following CVC use approximating 2-6%.^{9,10} At Intermountain Medical Center we have reported an annual rate of UEDVT ranging from 1.9-3%.^{11,12}

Because no randomized controlled studies have evaluated acute anticoagulation for initial treatment of UEDVT, evidence for the treatment of acute UEDVT is extrapolated from recommendations for treatment of lower extremity deep vein thrombosis (LEDVT).⁴ Prospective cohort studies have reported a clinically acceptable rate of recurrent thrombosis and hemorrhage when UEDVT is treated similarly to LEDVT (Table 2).¹³⁻¹⁵ Historically, the implementation of a parenteral anticoagulant (unfractionated heparin, low molecular weight heparin, fondaparinux) in conjunction with warfarin has been the mainstay for the treatment of acute venous thromboembolism (VTE). More recently, large prospective randomized clinical trials have demonstrated the comparative efficacy and safety of the direct oral anticoagulants (DOACs) apixaban, dabigatran, edoxaban, and rivaroxaban for the acute treatment¹⁶⁻²⁰ and secondary prevention^{17,21,22} of VTE. A pooled meta-analysis suggests DOACs compare favorably with LMWH/VKA for outcomes of recurrent VTE, pulmonary embolism (PE) mortality, and major bleeding.²³ Guidelines presently recommend therapeutic anticoagulation for a minimum duration of 3 months among patients with UEDVT⁴ and possibly longer should the thrombosis occur in the setting of a CVC which must remain in place. Recent level 1 evidence suggests that the DOAC edoxaban is safe and effective for the treatment of cancer-associated thrombosis (CAT).²⁴ Prospective randomized clinical trials assessing the safety and effectiveness of apixaban and rivaroxaban among patients with CAT are ongoing,²⁵⁻²⁷ and preliminary results suggest that the effectiveness of DOACs among patients with CAT may be a class-effect.^{28,29} Real-world experience with apixaban among patients with UEDVT and CAT would meaningfully inform clinical-decision-making, and contribute to the limited ongoing research among patients with UEDVT and cancer.^{30,31}

No evidence exists for the use of a DOAC for the treatment of UEDVT. Recurrent VTE among patients receiving a DOAC for the acute treatment of thrombosis is low (on-treatment rate of recurrent VTE 2%; 95% CI 1.6-2.4%). The rate compares favorably with the on-treatment rate of recurrent VTE (2.2%; 95% CI 1.8-3%) reported recently among patients with acute VTE treated with heparin/vitamin K antagonist (VKA).²³ Apixaban was compared with warfarin for the treatment of acute VTE.¹⁸ In a randomized double-blind study apixaban (at a dose of 10 mg twice daily for 7 days, followed by 5 mg twice daily for 6 months) was compared with conventional therapy (subcutaneous enoxaparin, followed by warfarin) in 5395 patients with acute VTE. Recurrent symptomatic VTE or death related to VTE occurred in 59 of 2609 patients (2.3%) in the apixaban group, as compared with 71 of 2635 (2.7%) in the conventional-therapy group (relative risk, 0.84; 95% confidence interval [CI], 0.60 to 1.18). Apixaban was noninferior to conventional therapy ($P < 0.001$). In this same study major bleeding occurred in 0.6% of the 2609 patients in the apixaban group, compared with 1.8% the 2635 patients in the conventional therapy group (relative risk, 0.31; 95% CI, 0.17 to 0.55; $P < 0.001$ for superiority). The composite outcome of major bleeding and clinically relevant nonmajor bleeding occurred in 4.3% of the patients in the apixaban group, as compared with 9.7% of those in the conventional therapy group (relative risk, 0.44; 95% CI, 0.36 to 0.55; $P < 0.001$). Evidence of efficacy for the treatment of UEDVT with an oral anticoagulant that requires no monitoring and delivers reliable therapeutic anticoagulation would be of great interest; and would be applicable to large number of patients. Apixaban, a selective direct factor

Xa inhibitor is believed to terminate the burst of thrombin generation and result in inhibition of thrombus formation and in clinical use has been observed to have a favorable safety profile.

4.0 STUDY HYPOTHESIS:

We hypothesize that apixaban 10mg BID for 7 days followed by apixaban 5 mg BID for 12 weeks will be noninferior to the rate of recurrent VTE and VTE related death as reported in the literature should the event rate we observe exclude 4%. We will also report how the event rate we observe compares to a historical control of case matched patients for the primary efficacy outcome recurrent symptomatic VTE and VTE-related death.

4.1 Study hypothesis for primary outcome:

The primary efficacy outcome will be the 90-day rate of clinically overt recurrent symptomatic VTE and VTE-related death.

4.2 Study hypothesis for primary safety outcome:

The primary safety outcome will be the combined 90-day rate of major bleeding and clinically-relevant non-major bleeding as formerly defined.¹⁸ For the composite outcome of major bleeding and clinically relevant nonmajor bleeding assuming a rate reported in the literature of 9.7%, should we observe the upper bound of the 95% confidence interval for event rate excludes 13%, we will consider apixaban as noninferior to warfarin.

4.3 Study hypothesis for secondary outcomes:

Additional outcomes will include all-cause mortality, VTE-related mortality, vein-specific quality of life assessment as measured by a standardized questionnaire,³ anticoagulant use quality of life assessment as measured by a standardized questionnaire¹ and post-thrombotic syndrome measured using a standardized technique.²

4.4 Ascertainment of historical control:

EMR interrogation implementing techniques we have previously performed and reported will identify patients that will serve as a historical control.^{32,33} Historical control patients will be ascertained from the timeframe prior to the FDA approval of DOACs (1 November 2010). This timeline is chosen so that there is not selection bias for the application of warfarin after DOAC approval. For each patient prospectively enrolled, we will match the maximal number of controls based upon age at the time of diagnosis, sex, and service line at the time of diagnosis (Emergency department vs. inpatient vs. inpatient ICU vs. outpatient). Matching reduces the possibility of severe loss of efficiency due to a major discrepancy in the empiric distributions of a strong risk factor between cases and controls.³⁴ All patients included in the historical control will have had 12 weeks of therapeutic anticoagulation. We will not limit the number of controls that may be matched with each individual patient.

5.0 RATIONALE FOR STUDY DESIGN

We will perform a prospective open label single arm cohort study with our primary outcome being the 90-day rate of new and/or recurrent objectively confirmed symptomatic VTE and VTE-related death compared to the reference value in the literature. Upon literature review, this was found to be 1.5% (see Table 2). Therefore if the event rate we observe excludes 4%, we will assume noninferiority. As a secondary outcome we will also report the rate we observe as it compares with a historical control of case matched patients derived from interrogation of our EMR. A control arm comprised of patients cared for within our healthcare system will better control for any arcane characteristics of patient management and thrombosis events unique to our environment and population. The adoption of a historical control from within our healthcare system provides the benefit of a “real-world” comparator.

6.0 STUDY POPULATION:

Consecutive patients identified with acute UEDVT presenting to the Intermountain Healthcare network and to the University of Utah Healthcare will be eligible for enrollment. The Intermountain Medical Center (IMC) is the flagship 440 bed tertiary care academic hospital of Intermountain Healthcare (IHC) located in Murray, Utah. The University of Utah Hospital is the 527 bed flagship hospital of University of Utah Healthcare and is a tertiary care center located in Salt Lake City, UT. Potentially eligible patients will be identified through the peripheral vascular labs and clinical service lines at the Intermountain Medical Center and University Hospital. Patients who provide signed informed consent will be eligible to participate. Patients eligible for enrollment will include those for whom acute UEDVT is identified upon compression ultrasound performed using the classic method³⁵ to assess venous compressibility, except in veins inaccessible to compression (e.g. the subclavian vein), in which case lumen echogenicity and Doppler flow characteristics will be used. Examination will consist of comprehensive venous compression, color flow imaging of the upper extremity including the proximal upper extremity deep veins (internal jugular vein, subclavian vein, axillary vein, brachial vein), distal upper extremity deep veins (radial vein, ulnar vein) and upper extremity superficial veins (basilic, cephalic) at 2-cm intervals in the transverse plane. Ultrasound results will be categorized as: (1) Normal (No DVT) if all imaged venous segments are fully compressible, or if there is absence of intraluminal echogenic material and normal flow in veins inaccessible to compression; (2) Inadequate for interpretation; (3) Abnormal defined as a non-compressible segment being present in the internal jugular vein, subclavian vein, axillary vein, brachial vein, ulnar vein, or radial vein, or echogenic material with evidence of compromised flow in segments inaccessible to compression.

6.1 Inclusion Criteria:

We will enroll patients with a diagnosis of acute upper extremity DVT as defined above in section 6.0. We will provide a Spanish language short form to facilitate enrollment of native Spanish-speaking patients. Patients with concomitant DVT for which the most proximal thrombus resides in the distal circulation are eligible. Otherwise concomitant venous thrombosis of another anatomic location or pulmonary embolism are ineligible. Patients must fulfill all of the following criteria for this study:

- 6.1.1 Be ≥ 18 years of age
- 6.1.2 Have received no more than six (6) doses of any therapeutic anticoagulant, or intravenous and therapeutic bridging heparin for longer than 72 hours
- 6.1.3 Women of childbearing potential (WOCBP) must have a negative serum or urine pregnancy test (minimum sensitivity 25 IU/L or equivalent units of HCG) within 24 hours prior to the start of study drug.
- 6.1.4 Women must not be breastfeeding
- 6.1.5 WOCBP must agree to follow instructions for method(s) of contraception for the duration of treatment with study drug apixaban plus 5 half-lives of study drug apixaban (3 days) plus 30 days (duration of ovulatory cycle) for a total of 33 days post-treatment completion.
- 6.1.6 Males who are sexually active with WOCBP must agree to follow instructions for method(s) of contraception for the duration of treatment with study drug apixaban plus 5 half-lives of the study drug apixaban (3 days) plus 90 days (duration of sperm turnover) for a total of 93 days post-treatment completion.
- 6.1.7 Azoospermic males and WOCBP who are continuously not heterosexually active are exempt from contraceptive requirements. However WOCBP must still undergo pregnancy testing as described in this section.

Investigators shall counsel WOCBP and male subjects who are sexually active with WOCBP on the importance of pregnancy prevention and the implications of an unexpected pregnancy. Investigators shall advise WOCBP and male subjects who are sexually active with WOCBP on the use of highly effective methods of contraception. Highly effective methods of contraception have a failure rate of $< 1\%$ when used consistently and correctly.

At a minimum, subjects must agree to the use of one method of highly effective contraception.

6.2 Exclusion Criteria:

- 6.2.1 Another indication for long-term anticoagulation for which no FDA approval of apixaban exists (e.g. prosthetic heart valves)
- 6.2.2 Life expectancy of less than 6 months
- 6.2.3 Unable to engage in reliable follow-up as per protocol
- 6.2.4 Participating in a clinical trial or has participated in a clinical trial within the last 30 days
- 6.2.5 Receiving concomitant dual antiplatelet therapy
- 6.2.6 Requires aspirin dose of greater than 165mg daily
- 6.2.7 A hemoglobin level of less than 8 mg per deciliter
- 6.2.8 A platelet count of less than 50,000 per cubic millimeter
- 6.2.9 A calculated creatinine clearance of less than 25 mL per minute
- 6.2.10 Alanine aminotransferase or aspartate aminotransferase level greater than 2 times the upper limit of the normal range


- 6.2.11 A total bilirubin more than 1.5 times the upper limit of the normal range.
- 6.2.12 For patients receiving ELIQUIS 5 mg or 10 mg twice daily, the dose of ELIQUIS should be decreased by 50% when coadministered with drugs that are strong dual inhibitors of CYP3A4 and P-gp (e.g., ketoconazole, itraconazole, ritonavir, or clarithromycin) [see Package Insert Dosage and Administration (2.5) and Clinical Pharmacology (12.3)]. For patients receiving ELIQUIS at a dose of 2.5 mg twice daily, avoid coadministration with strong dual inhibitors of CYP3A4 and P-gp.
- 6.2.13 Intend pregnancy or breastfeeding within the next year
- 6.2.14 Known allergy to apixaban, rivaroxaban, or edoxaban
- 6.2.15 Active pathological bleeding.
- 6.2.16 Any condition that at the discretion of the investigator is thought to prohibit active participation and follow-up in the trial
- 6.2.17 UEDVT that occurs while therapeutic anticoagulation is being taken by the patient (“event on therapy”)
- 6.2.18 The patient has concomitant VTE diagnosed elsewhere except deep vein thrombosis that has its most proximal aspect in the distal veins (“isolated distal DVT”).

7.0 STUDY INTERVENTION

Patients will have a blood draw to affirm renal and liver function if these laboratory values have not been obtained clinically. We will obtain CBC and CMP laboratory values. Patients with acute UEDVT who meet eligibility criteria and provide informed consent will receive apixaban 10 mg PO BID for 7 days, followed by 5 mg PO BID for a duration of 11 weeks. Apixaban will be provided by Bristol-Myers-Squibb (BMS). Apixaban will be shipped to the study site and dispensed at the time of enrollment by the study group. Adequate apixaban will be dispensed for the complete 12-week course of therapy. Should a patient lose doses, these will be replaced at no expense to the patient. Should study drug be lost repeatedly, then a follow-up mechanism for dispensing study drug at shorter intervals will be pursued at the discretion of the investigator. Apixaban will be initiated for the treatment of acute venous thromboembolism as per FDA approved package insert.³⁶

7.1 Apixaban packaging, labeling, and storage:

Apixaban will be provided by BMS to the study center in 5-mg tablets (#60 per bottle). They will be stored under the discretion of the investigational pharmacy and dispensed at the investigator's discretion per study protocol. Inventory, reordering, and destruction will be managed by the investigational pharmacy. Drug labeling will be according to national law. Apixaban will be stored at room temperature (see Table below).

PRODUCT	Packaging	APPEARANCE	Storage and handling
Apixaban 5-mg tablets	Commercial Bottle of 60	Pink, oval, biconvex, film coated tablets with "894" debossed on one side and "5" on the other side 	Store at 20°C to 25°C (68°F-77°F); excursions permitted between 15°C and 30°C (59°F-86°F) [see USP Controlled Room Temperature].

If concerns regarding the quality or appearance of the investigational product arise, do not dispense the investigational product, and contact BMS immediately.

8.0 STUDY FOLLOW-UP SCHEDULE

Scheduled visits associated with the study will include the initial screening visit at the time of UEDVT diagnosis, and the 90 day follow-up visit. See Table 1 below for schedule of events at each visit. All patients will receive follow-up at or around 12 weeks of treatment. Every attempt will be made to see the patient at 12 weeks. If the patient is unable to present, then a telephone call or electronic (email) questionnaire completion will suffice as adequate 12-week follow-up. The link to the email questionnaire will be sent to the patient's personalized email at the request of the patient. A standardized questionnaire assessing for primary and secondary outcomes will be administered at 12 weeks. Any therapy beyond the 12-week study period will be administered per clinical routine. The study will be complete after the 12-week follow-up.

Table 1: Table of scheduled events		
	Enrollment	90-day follow-up visit
Obtain informed consent	X	
Dispense 12-weeks of study drug	X	
Diagnostic ultrasound	X	
Administer anticoagulant QOL questionnaire		X
Administer VEINES QOL questionnaire	X	X
Assessment for post-thrombotic syndrome	X	X
Assessment for primary and secondary outcomes using a standardized form		X
Pill count of study drug		X
Complete study		X

9.0 SAMPLE SIZE AND POWER CALCULATION

Literature review was performed to ascertain an event rate that would allow for sample size estimate. We estimate a 90 day rate of recurrent VTE and VTE-related death of 1.5%, based on recurrent VTE from prior observational studies (Table 2). A sample size of 357 patients who meet eligibility criteria was chosen so that an exact 95% confidence interval would exclude an event rate of 4% for 90-day recurrent symptomatic venous thrombosis and venous thromboembolism-related death. Excluding an event rate of 4% is the commonly accepted standard by which diagnostic strategies are deemed clinically acceptable. Anticipating a 5% rate of withdrawal, a total of 375 patients will be enrolled.

10.0 STATISTICAL ANALYSIS

In our primary analysis a two-sided confidence interval for the event rate (objectively verified VTE + VTE-related death) will be calculated for the observation cohort by exact methods. If the confidence interval for the event excludes the commonly accepted threshold event rate of 4%, we will conclude that treatment with apixaban is noninferior to the reference value in the literature, and therefore a clinically valid approach to treat UEDVT. Additionally, thrombosis and bleeding rates among patients with cancer-associated thrombosis will be reported separately. As a secondary analysis we will also compare the event rates of clinically important outcomes (recurrent symptomatic venous thrombosis, venous thromboembolism-related death, and major and clinically relevant nonmajor bleeding) to a historical control of case matched patients. We will reserve matching only for risk factors whose confounding effects need to be controlled for but that are not of scientific interest as independent risk factors in the study. Age and sex are often used as matching variables because they are usually strong confounders and because their effects are usually well known from descriptive epidemiology. We anticipate matching enrolled patients to those from the historical control group on the following important variables whose confounding effects need to be controlled for: age, sex, and presentation service line (Emergency department, inpatient, and outpatient). The relationship between the outcomes and apixaban treatment, controlled for cancer-associated thrombosis, will be analyzed using conditional logistic regression, which accounts for the paired nature of the data introduced by matching.

11.0 STUDY OUTCOME ASCERTAINMENT

The primary efficacy and primary safety outcomes (2.1, 2.2) identified among patients prospectively enrolled will be evaluated by three independent adjudicators. Upon review interobserver agreement will be reported using a K statistic. Any disagreement will be decided upon discussion and consensus. To limit inter-observer variability, patient information will be redacted and entered in specific data fields on a form generated for this purpose in a Case Report Form for events identified both in the study and historical control cohorts. Venous thromboembolism will be defined as DVT or PE that has been objectively confirmed by a Doppler US, venography, pulmonary-perfusion scan, spiral CT scan, MRI, or pulmonary angiogram; an elevated D-Dimer test will not be sufficient for a diagnosis of VTE. Information regarding the treatment and management of UEDVT will be provided as per clinical routine.

Study Outcomes for adjudication
Upper extremity DVT
Bleeding reported during the clinical trial

The criteria for interpretation of test results by the adjudication panel will be standardized in the following fashion:

11.1 Evaluation of suspected outcome event of UEDVT:

Evaluation of suspected UEDVT will occur at the discretion of the clinician caring for the patient. Acute or recurrent UEDVT will be identified upon compression ultrasound performed using the classic method³⁵ to assess venous compressibility; or lumen echogenicity and Doppler flow

characteristics in segments not amenable to compression. Examination will consist of comprehensive venous compression, color flow imaging, and pulse wave evaluation with augmentation of the upper extremity including the proximal upper extremity deep veins (internal jugular vein, subclavian vein, axillary vein, brachial vein), distal upper extremity deep veins (radial vein, ulnar vein) and upper extremity superficial veins (basilic, cephalic) at 2-cm intervals in the transverse plane. Ultrasound results will be categorized as:

- Normal (No DVT) if all imaged venous segments are fully compressible.
- Inadequate for interpretation
- Abnormal defined as a non-compressible segment being present in the internal jugular vein, subclavian vein, axillary vein, brachial vein, ulnar vein, or radial vein; or abnormal lumen echogenicity and Doppler flow characteristics in segments not amenable to compression.

Recurrent thrombosis will be considered present if: (1) in the setting of a clinical indication to perform a study there is a new non-compressible venous segment in the aforementioned anatomic distributions defined as a radiographic extension at the margin of prior thrombosis greater than 1 cm, or abnormal lumen echogenicity and Doppler flow characteristics in segments not amenable to compression, or overt pulmonary embolism defined per clinical routine. If new superficial venous thrombosis (SVT) is diagnosed, it will be recorded however it will not count toward the primary efficacy outcome.

These same metrics will be used by an adjudication committee for the comparator arm.

11.2 Evaluation of suspected outcome event of LEDVT:

Evaluation of suspected LEDVT will occur at the discretion of the clinician caring for the patient. Compression ultrasound will be performed using the classic method,³⁵ and compressibility of the veins will be assessed. Examination will consist of comprehensive venous compression, color flow imaging, and pulse wave evaluation with augmentation of the common femoral, superficial femoral, popliteal veins, and calf veins at 2-cm intervals in the transverse plane. Ultrasound results will be categorized as:

- Normal (No DVT):
 - all imaged venous segments are fully compressible
- Inadequate for Interpretation
- Abnormal:
 - noncompressible segment is identified

New thrombosis will be considered present if:

- there is a non-compressible iliac, common femoral, superficial femoral, deep femoral or popliteal vein;

- if a prior ultrasound is available for comparison, new thrombosis will be considered present if there exists:
 - a new non-compressible iliac, common femoral or popliteal vein, or
 - a radiographic extension at the margin of prior thrombosis greater than 1 cm at the common femoral or popliteal sites, or

If isolated distal (calf vein) DVT is diagnosed, this will be recorded however will not serve as contributory to the primary outcome. Per clinical routine a second ultrasound of the proximal deep veins will be repeated after 1 week to determine if the above diagnostic criteria have occurred as per clinical recommendations.^{37,38}

Deep venous thrombosis in an unusual locations (cerebral vein, porto-mesenteric veins, gonadal veins, etc.) will be recorded however will not be counted for the primary efficacy outcome. These same metrics will be used by an adjudication committee for the comparator arm.

11.3 Evaluation and diagnosis of suspected outcome event of pulmonary embolism:

Evaluation of suspected PE will occur at the discretion of the clinician caring for the patient. Pulmonary embolism will be considered present if there is PE defined on a computed tomography pulmonary arteriography (CTPA) (contrast material outlining an intraluminal defect or a vessel occluded by low attenuation material) read by a board-certified radiologist. Pulmonary embolism will also be considered present if there is PE defined on a pulmonary ventilation-perfusion (V/Q) scan which will be interpreted as positive in the setting of a high probability V/Q lung scan in a patient with no prior PE, and high or intermediate pre-test probability for PE by a clinical assessment, or a positive venous ultrasound in a patient with no prior LEDVT in a patient with a nondiagnostic V/Q scan and high or intermediate clinical probability by a pretest probability score (e.g. Wells criteria, Revised Geneva Score). This is a surrogate for the diagnosis of PE that others have described.³⁹ Pulmonary embolism will also be considered present if PE is defined on pulmonary angiography as an angiogram with an embolus obstructing a vessel or the outline of an embolus (filling defect) within a pulmonary artery as others have previously described.⁴⁰ Should the unlikely event occur that the clinician chooses MRI to investigate PE then pulmonary embolism will be considered present if there was PE defined on an MRI which is often described as partially occlusive intraluminal filling which may be shown as “railway tracking”, i.e. a small amount of contrast material between the central filling defect and the arterial wall or, in cross sectional images, as a filling defect surrounded by contrast material; or complete arterial occlusion with termination of the column of contrast material in a meniscus that outlines the trailing edge of the embolus.³⁹ Should a patient have a history of PE and present with symptoms worrisome for recurrent PE, and if there is a (new) "high probability" perfusion defect or a new intraluminal filling defect, (should a previous study available for comparison) then PE will be diagnosed.⁴¹ Should there be a former study for comparison, PE will be excluded if there is no new perfusion defect or intraluminal filling defect.

These same metrics will be used by an adjudication committee for the comparator arm.

11.4 Evaluation and diagnosis of thromboembolism-related death:

Cause of death will be based on information provided by attending physicians and/or relatives and, when available, using the results of autopsy. Pulmonary embolism will be considered the cause of death if there is objective documentation for PE or if death could not be attributed to another documented cause and pulmonary embolism could not be ruled out as others have similarly reported.¹⁸ All-cause death will also be reported.

These same metrics will be used by an adjudication committee for the comparator arm.

11.5 Evaluation and diagnosis of suspected bleeding:

Patients will be asked to report any bleeding and will be routinely questioned regarding bleeding events at each scheduled telephone call and clinic visit. Bleeding will be classified as major, clinically relevant nonmajor, or nuisance bleeding. We define major bleeding in a standardized fashion⁴² as performed by others,^{18,21} as clinically overt bleeding accompanied by one or more of the following: a decrease in the hemoglobin level of 2 g per deciliter or more over a 24-hour period, transfusion of 2 or more units of packed red cells, bleeding at a critical site (intracranial, intraspinal, intraocular, pericardial, intraarticular, intramuscular with compartment syndrome, or retroperitoneal), or fatal bleeding. Clinically relevant nonmajor bleeding will be defined as clinically overt bleeding that does not satisfy the criteria for major bleeding and that led to hospital admission, physician-guided medical or surgical treatment, or a change in antithrombotic therapy.⁴³ Nuisance bleeding will be defined as any other bleeding reported by the patient that does not meet the aforementioned criteria for major bleeding or clinically relevant nonmajor bleeding, and will be recorded. We will report for the analyses of bleeding events all patients who received at least one dose of a study drug and include all events from the time the first dose of a study drug was received until 2 days after the last dose was received as has performed by others.⁴³ EMR interrogation will allow us to assess for these same metrics in the control population to define major bleeding as we have previously performed. Suspected outcomes of bleeding or clinically relevant nonmajor bleeding will be reviewed and adjudicated by a committee.

11.6 Evaluation of patient satisfaction:

Patient satisfaction will be measured at the end of study treatment using the Anti-Clot Treatment Scale (ACTS) which is a validated patient satisfaction questionnaire that was derived¹ and implemented⁴⁴ comparing a novel oral anticoagulant to warfarin. Outcomes of patient satisfaction will be recorded using a standardized form.

11.7 Evaluation of post thrombotic syndrome:

Little is known about the rate of post-thrombotic syndrome after treatment of UEDVT. Post thrombotic syndrome will be assessed in person at the 12 week follow-up visit. Patients will complete a modified version of a standardized post thrombotic syndrome severity assessment questionnaire (Villalta Scale).²

11.8 Disease specific quality of life:

Disease-specific quality of life will be assessed in all patients at enrollment and at study visits using the VEINES-QOL instrument.³

Ultimately all outcomes, with the exception of the secondary outcomes ascertained by survey will be adjudicated by a panel of vascular medicine specialists.

12.0 ETHICAL CONSIDERATIONS

12.1 Good Clinical Practice:

This study will be conducted in accordance with Good Clinical Practice (GCP), as defined by the International Conference on Harmonisation (ICH) and in accordance with the ethical principles underlying European Union Directive 2001/20/EC and the United States Code of Federal Regulations, Title 21, Part 50 (21CFR50).

The study will be conducted in compliance with the protocol. The protocol, any amendments, and the subject informed consent will receive Institutional Review Board/Independent Ethics Committee (IRB/IEC) approval/favorable opinion before initiation of the study.

All potential serious breaches must be reported to Bristol-Myers Squibb (BMS) immediately. A serious breach is a breach of the conditions and principles of GCP in connection with the study or the protocol, which is likely to affect, to a significant degree, the safety or physical or mental integrity of the subjects of the study or the scientific value of the study.

Study personnel involved in conducting this study will be qualified by education, training, and experience to perform their respective tasks.

This study will not use the services of study personnel where sanctions have been invoked or where there has been scientific misconduct or fraud (e.g., loss of medical licensure; debarment).

12.2 Institutional Review Board/Independent Ethics Committee:

Before study initiation, the investigator must have written and dated approval/favorable opinion from the IRB/IEC for the protocol, consent form, subject recruitment materials/process (e.g., advertisements), and any other written information to be provided to subjects. The investigator or sponsor should also provide the IRB/IEC with a copy of the Investigator Brochure or product labeling information to be provided to subjects, and any updates.

The investigator should provide the IRB/IEC with reports, updates, and other information (e.g., expedited safety reports, amendments, and administrative letters) according to regulatory requirements or institution procedures.

12.3 Informed Consent and Study Discontinuation:

Investigators must ensure that subjects or, in those situations where consent cannot be given by subjects, their legally acceptable representative are clearly and fully informed about the purpose, potential risks, and other critical issues regarding clinical studies in which they volunteer to participate.

Investigators must:

- a) Provide a copy of the consent form and written information about the study in the language in which the subject is most proficient prior to clinical study participation. The language must be non-technical and easily understood.
- b) Allow time necessary for subject or subject's legally acceptable representative to inquire about the details of the study.
- c) Obtain an informed consent signed and personally dated by the subject or the subject's legally acceptable representative and by the person who conducted the informed consent discussion.
- d) Obtain the IRB/IEC's written approval/favorable opinion of the written informed consent form and any other information to be provided to the subjects, prior to the beginning of the study, and after any revisions are completed for new information.
- e) If informed consent is initially given by a subject's legally acceptable representative or legal guardian, and the subject subsequently becomes capable of making and communicating their informed consent during the study, then consent must additionally be obtained from the subject.
- f) Revise the informed consent whenever important new information becomes available that is relevant to the subject's consent. The investigator, or a person designated by the investigator, should fully inform the subject or the subject's legally acceptable representative or legal guardian, of all pertinent aspects of the study and of any new information relevant to the subject's willingness to continue participation in the study. This communication should be documented.

12.3.1 Women of childbearing potential

A woman of childbearing potential (WOCBP) is defined as any female who has experienced menarche and who has not undergone surgical sterilization (hysterectomy or bilateral oophorectomy) and is not postmenopausal. Menopause is defined as 12 months of amenorrhea in a woman over age 45 years in the absence of other biological or physiological causes. In addition, females under the age of 55 years must have a serum follicle stimulating hormone, (FSH) level > 40mIU/mL to confirm menopause.

*Females treated with hormone replacement therapy, (HRT) are likely to have artificially suppressed FSH levels and may require a washout period in order to obtain a physiologic FSH level. The duration of the washout period is a function of the type of HRT used. The duration of the washout period below are suggested guidelines and the investigators should use their judgement in checking serum FSH levels. If the serum FSH level is >40 mIU/ml at any time during the washout period, the woman can be considered postmenopausal:

- 1 week minimum for vaginal hormonal products (rings, creams, gels)
 - 4 week minimum for transdermal products
 - 8 week minimum for oral products
- Other parenteral products may require washout periods as long as 6 months.

12.3.2 Discontinuation of subjects from treatment

Subjects MUST discontinue investigational product (and noninvestigational product at the discretion of the investigator) for any of the following reasons:

- Withdrawal of informed consent (subject's decision to withdraw for any reason).
- Any clinical adverse event, laboratory abnormality, or intercurrent illness which, in the opinion of the investigator, indicates that continued participation in the study is not in the best interest of the subject.
- Pregnancy
 - Instruct WOCBP to contact the investigator or study staff immediately if they suspect they might be pregnant (e.g., missed or late menstrual period) at any time during study participation. Institutional policy and local regulations should determine the frequency of on-study pregnancy tests for WOCBP enrolled in the study.
 - The investigator must immediately notify BMS if a study subject becomes pregnant.
- Loss of ability to freely provide consent through imprisonment or involuntary incarceration for treatment of either a psychiatric or physical (e.g., infectious disease) illness.

All subjects who discontinue should comply with protocol-specified follow-up procedures outlined in Section 6. The only exception to this requirement is when a subject withdraws consent for all study procedures or loses the ability to consent freely (i.e., is imprisoned or involuntarily incarcerated for the treatment of either a psychiatric or physical illness). If a subject withdraws before completing the study, the reason for withdrawal must be documented appropriately.

13.0 ADVERSE EVENTS

An Adverse Event [AE] is defined as any new untoward medical occurrence or worsening of a pre-existing medical condition in a patient or clinical investigation subject administered an investigational (medicinal) product and that does not necessarily have a causal relationship with this treatment. An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding, for example), symptom, or disease temporally associated with the use of investigational product, whether or not considered related to the investigational product.

The causal relationship to study drug is determined by a physician and should be used to assess all adverse events (AEs). The causal relationship can be one of the following:

- Related: There is a reasonable causal relationship between study drug administration and the AE.
- Not Related: There is not a reasonable causal relationship between study drug administration and the AE.

The term “reasonable causal relationship” means there is evidence to suggest a causal relationship.

Adverse events can be spontaneously reported or elicited during open-ended questioning, examination, or evaluation of a subject. (In order to prevent reporting bias, subjects should not be questioned regarding the specific occurrence of one or more adverse events).

13.1 Serious Adverse Events

A **Serious Adverse Event (SAE)** is any untoward medical occurrence at any dose that:

- results in death
- is life-threatening (defined as an event in which the subject was at risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it were more severe)
- requires inpatient hospitalization or causes prolongation of existing hospitalization (see **NOTE***: below for exceptions)
- results in persistent or significant disability/incapacity
- is a congenital anomaly/birth defect
- is an important medical event, defined as a medical event that may not be immediately life-threatening or result in death or hospitalization but, based on appropriate medical and scientific judgment, may jeopardize the subject or may require intervention (e.g., medical, surgical) to prevent one of the other serious outcomes listed above. Examples of such events include but are not limited to intensive treatment in an emergency department or at home for allergic bronchospasm; blood dyscrasias or convulsions that do not result in hospitalization.

Suspected transmission of an infectious agent (e.g., pathogenic or non-pathogenic) via the study drug is an SAE.

Although pregnancy, overdose, and cancer are not always serious by regulatory definition, these events must be handled as SAEs.

***NOTE:** *The following hospitalizations are not considered SAEs:*

- A visit to the emergency room or other hospital department lasting less than 24 hours that does not result in admission (unless considered an “important medical event” or a life-threatening event)
- Elective surgery planned before signing consent
- Admissions as per protocol for a planned medical/surgical procedure
- Routine health assessment requiring admission for baseline/trending of health status (e.g., routine colonoscopy)
- Medical/surgical admission other than remedying ill health state that was planned before study entry. Appropriate documentation is required in these cases
- Admission encountered for another life circumstance that carries no bearing on health status and requires no medical/surgical intervention (e.g., lack of housing, economic inadequacy, caregiver respite, family circumstances, administrative reason)

Adverse Events of Special Interest

In this study, the following adverse events are to be reported to BMS, regardless of whether these reports are classified as serious or unexpected.

Potential or suspected cases of liver injury including but not limited to liver test abnormalities, jaundice, hepatitis or cholestasis.

13.1.1 Serious Adverse Event Collecting and Reporting

Following the subject’s written consent to participate in the study, all SAEs, whether related or not related to study drug, must be collected, including those thought to be associated with protocol-specified procedures. All SAEs must be collected that occur during the screening period and within 30 days of discontinuing dosing. If applicable, SAEs must be collected that relate to any later protocol-specific procedure (such as follow-up skin biopsy).

The investigator should report any SAE occurring after these time periods that is believed to be related to study drug or protocol-specified procedure.

SAE reports should be completed on a MedWatch Form 3500A for any event where doubt exists regarding its status of seriousness.

If the investigator believes that an SAE is not related to study drug, but is potentially related to the conditions of the study (such as withdrawal of previous therapy, or a complication of a study procedure), the relationship should be specified in the narrative section of the SAE Report Form.

SAEs, whether related or unrelated to the study drug, and pregnancies, must be reported to BMS within 24 hours. This initial notification may occur via e-mail; however, all SAE information thereafter must be recorded on the MedWatch Form 3500A which can be accessed at:

<https://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Forms/UCM048334.pdf>

Please send the MedWatch form BMS:

Global Pharmacovigilance & Epidemiology
Bristol-Myers Squibb Company
Fax Number: 609-818-3804
Email: Worldwide.safety@bms.com

If only limited information is initially available, follow-up reports are required. (Note: Follow-up SAE reports should include the same investigator term(s) initially reported.) If an ongoing SAE changes in its intensity or relationship to study drug or if new information becomes available, a follow-up MedWatch Form 3500A, or Pregnancies Surveillance Form, should be sent within 24 hours to the BMS (or designee) using the same procedure used for transmitting the initial SAE report.

All SAEs should be followed to resolution or stabilization.

13.1.2 SAE Reconciliation

The investigator will reconcile the clinical database SAE cases transmitted to BMS Global Pharmacovigilance (GPV&E). Frequency of reconciliation will be every three months and once prior to study database lock. BMS GPV&E will e-mail upon request from the investigator, the GPV&E reconciliation report. Requests for reconciliation should be sent to aepbusinessprocess@bms.com. The data elements listed on the GPV&E reconciliation report will be used for case identification purposes. If the investigator determines a case was not transmitted to BMS GPV&E, the case will be sent immediately.

13.1.3 Health Authority Reporting (US FDA IND)

Investigators must adhere to local Health Authority Reporting Requirements. Per the IND Exemption, ARM-DVT meets all of the requirements for exemption from the IND regulations, and the FDA has granted this exemption. Therefore, an IND is not required to conduct investigation of Apixaban and any future serious adverse events should not be submitted to the FDA.

13.2 Non-serious events

A nonserious adverse event is an AE not classified as serious.

13.2.1 Non-Serious Adverse Events (NSAEs) Collecting and Reporting

The collection of non-serious adverse event (NSAE) information should begin at initiation of study drug. Nonserious adverse event information should also be collected from the start of a placebo lead-in period or other observational period intended to establish a baseline status for the subjects.

Nonserious AEs should be followed to resolution or stabilization, or reported as SAEs if they become serious. Follow-up is also required for nonserious AEs that cause interruption or discontinuation of study drug, or those that are present at the end of study treatment as appropriate.

Nonserious Adverse Events are provided to BMS via annual safety reports (if applicable), and interim or final study reports.

13.3 Laboratory Test Abnormalities

The following laboratory abnormalities should be captured and reported as appropriate:

- Any laboratory test result that is clinically significant or meets the definition of an SAE
- Any laboratory test result abnormality that required the subject to have study drug discontinued or interrupted
- Any laboratory test result abnormality that required the subject to receive specific corrective therapy.

It is expected that wherever possible, the clinical rather than the laboratory term will be used by the reporting investigator (e.g., use the term anemia rather than low hemoglobin value).

Laboratory test abnormalities are provided to BMS via annual safety reports (if applicable), and interim or final study reports.

13.4 Pregnancy

If, following initiation of the investigational product, it is subsequently discovered that a study subject is pregnant or may have been pregnant at the time of investigational product exposure, including during at least 5 half-lives after product administration, the investigational product will

be permanently discontinued in an appropriate manner (e.g., dose tapering if necessary for subject safety).

The investigator must immediately notify WorldwideSafety@BMS.com of this event via the Pregnancy Surveillance Form within 24 hours and in accordance with SAE reporting procedures. Follow-up information regarding the course of the pregnancy, including perinatal and neonatal outcome and, where applicable, offspring information must be reported on a Pregnancy Surveillance Form.

Any pregnancy that occurs in a female partner of a male study participant should be reported to BMS. Information on this pregnancy may also be collected on the Pregnancy Surveillance Form.

Protocol-required procedures for study discontinuation and follow-up must be performed on the subject unless contraindicated by pregnancy (e.g., x-ray studies). Other appropriate pregnancy follow-up procedures should be considered if indicated.

13.5 Overdose

An overdose is defined as the accidental or intentional administration of any dose of a product that is considered both excessive and medically important. All occurrences of overdose must be reported as SAEs.

13.6 Other Safety Considerations

Any significant worsening noted during interim or final physical examinations, electrocardiograms, X-rays, and any other potential safety assessments, whether or not these procedures are required by the protocol, should also be recorded as a nonserious or serious adverse event, as appropriate, and reported accordingly.

13.7 Compliance with the Protocol

The study shall be conducted as described in this approved protocol. All revisions to the protocol must be discussed with, and be prepared by, BMS. The investigator should not implement any deviation or change to the protocol without prior review and documented approval/favorable opinion from the IRB/IEC of an amendment, except where necessary to eliminate an immediate hazard(s) to study subjects.

If a deviation or change to a protocol is implemented to eliminate an immediate hazard(s) prior to obtaining IRB/IEC approval/favorable opinion, as soon as possible the deviation or change will be submitted to:

- IRB/IEC for review and approval/favorable opinion
- Bristol-Myers Squibb
- Regulatory Authority(ies), if required by local regulations

Documentation of approval signed by the chairperson or designee of the IRB(s)/IEC(s) must be sent to BMS.

If an amendment substantially alters the study design or increases the potential risk to the subject: (1) the consent form must be revised and submitted to the IRB(s)/IEC(s) for review and approval/favorable opinion; (2) the revised form must be used to obtain consent from subjects currently enrolled in the study if they are affected by the amendment; and (3) the new form must be used to obtain consent from new subjects prior to enrollment.

If the revision is an administrative letter, investigators must inform their IRB(s)/IEC(s).

13.7.1 Study Drug Records

It is the responsibility of the investigator to ensure that a current disposition record of investigational product (those supplied by the BMS) is maintained at each study site where study drug and noninvestigational product(s) is/are inventoried and dispensed. Records or logs must comply with applicable regulations and guidelines and should include:

- amount received and placed in storage area
- amount currently in storage area
- label ID number or batch number
- amount dispensed to and returned by each subject, including unique subject identifiers
- amount transferred to another area/site for dispensing or storage
- non-study disposition (e.g., lost, wasted)
- amount destroyed at study site, if applicable
- amount returned to the BMS
- retain samples for bioavailability/bioequivalence, if applicable
- dates and initials of person responsible for Investigational Product (IP) dispensing/accountability, as per the Delegation of Authority Form.

13.8 Destruction of Investigational Product

If the study drugs are to be destroyed on site, it is the investigator's responsibility to ensure that arrangements have been made for disposal, and that procedures for proper disposal have been established according to applicable regulations, guidelines, and institutional procedures. Appropriate records of the disposal must be maintained.

14.0 PREMATURE DISCONTINUATION OR INTERRUPTION OF ANTICOAGULATION

Patients may be withdrawn from the study for the following reasons:

- At their own request or at the request of their legally acceptable representative.

- If, in the investigator's opinion, continuation in the study would be detrimental to the subject's well-being.
- At the specific request of the investigator.

Early, permanent discontinuation of study drug is discouraged wherever possible. The single most important reason for premature discontinuation will be marked on the appropriate CRF and in the subject medical records. Discontinued patients will not be replaced. All subjects who discontinue should comply with protocol-specified follow-up procedures; the only exception to this requirement is when a subject withdraws consent for all study procedures or loses the ability to consent freely.

In some situations, it might be necessary to interrupt study medication temporarily (e.g. while contraindicated medication is taken, or for an invasive procedure). Patients should be encouraged to restart study drug after a short interruption except when absolutely contraindicated. Any interruption should occur as per clinical routine with resumption of anticoagulation when considered clinically safe and acceptable per clinical routine. Apixaban will be discontinued at least 48 hours prior to elective surgery or invasive procedures with a moderate or high risk of unacceptable or clinically significant bleeding. Apixaban will be discontinued at least 24 hours prior to elective surgery or invasive procedures with a low risk of bleeding or where the bleeding would be non-critical in location and easily controlled. Bridging anticoagulation during the 24 to 48 hours after stopping apixaban and prior to the intervention is not generally required. Apixaban will be restarted after the surgical or other procedures as soon as adequate hemostasis has been established.

15.0 DATA MANAGEMENT

Data will be managed at the Intermountain Medical Center (IMC) under the supervision of a staff statistician, employed by Intermountain Healthcare. All data will reside behind a password protected firewall with accessible only to study personnel.

16.0 SUBSTUDIES

Substudies at the discretion of the investigators may be performed to help elucidate optimal diagnosis, management, and treatment of UEDVT and related conditions. Informed consent will be obtained for collection and use of any data and/or study samples for future research to be determined.

17.0 MINIMIZATION OF BIAS

Selective enrollment of patients: Consecutive patients that meet eligibility criteria and provide informed consent will be approached for consent, and all eligible consenting subjects enrolled and randomized without exception.

Biased assessment of clinical outcomes: Evaluation of suspected VTE and bleeding will occur in a standard manner. Strict diagnostic criteria and subsequent interpretation by an independent adjudication panel will guard against differential interpretation of these tests. A kappa statistic will be reported to ascertain for interobserver agreement. To avoid a biased historical control arm all

consecutive qualified patients identified with UEDVT prior to the advent of Food and Drug Administration approval of DOACs (1 January 2011). Outcomes of 90-day new or recurrent VTE and major bleeding and clinically relevant nonmajor bleeding will be verified and recorded for adjudication.

Incomplete follow-up: Patient registration into a central study cohort will identify subjects enrolled. Upon the provision of initial patient informed consent, family members and referring physicians may be contacted if there is difficulty contacting patients during follow-up.

18.0 INFORMED CONSENT

The investigator, or person designated by the investigator will assume responsibility that the patient is clearly and fully informed about the purpose, potential risks, and other critical issues regarding their participation in the study in language and terms they are able to understand. Patients will be informed about their right to withdraw from the trial at any time, and necessary time will be allowed for the patient to inquire about the details of the study. Freely given written informed consent will be obtained from every study patient prior to study participation. The approved, written consent form document must be signed and personally dated by the study patient and by the person who conducted the informed consent discussion. A copy of the signed and dated written consent form document and any other written information will be provided to the patient. No patient will be enrolled that is not capable of performing their own informed consent.

19.0 SAFETY MONITORING

This study will be conducted in accordance with the guiding principles detailed in the Declaration of Helsinki (Helsinki, Finland 1964) and all applicable amendments. Study personnel involved in conducting this study will be qualified by education, training and experience to perform their respective task(s) and will continuously monitor subject safety, specifically ascertaining adverse events. To assure the safety of patients enrolled we will empanel a Safety Monitoring Committee (SMC). The SMC will meet after the first 20 patients are enrolled and then with enrollment of patients number 50, 100, 150, and 200, and ad hoc at the discretion of the chair of the SMC. The charter of the SMC is attached to IRB submitted documentation. All outcome events, serious adverse events, and nonserious adverse events will be communicated to the Intermountain Healthcare IRB per requisite agreement.

20.0 INSTITUTIONAL REVIEW BOARD

Prior to the commencement of the trial written and dated approval from the Intermountain Healthcare Institutional Review Board (IRB) and or study deference from the University of Utah IRB to the Intermountain Healthcare IRB will be obtained for the study protocol, consent forms, recruitment materials, and other written information that will be provided to study subjects.

21.0 ADJUDICATION OF OUTCOME EVENTS

All outcomes of thrombosis and bleeding that occur during the prospective study and that are identified in the historical control group will be adjudicated three independent adjudicators. Each individual will have established expertise in vascular medicine will be named to adjudicate all suspected events of DVT

or PE, and all diagnostic tests for these occurring during the follow-up period. The *kappa* statistic of interobserver agreement will be reported as similarly performed by others⁴⁵ and discussion leading to consensus will resolve disputes. All deaths will be adjudicated as to whether attributable to venous thrombosis, bleeding, or another cause by the same group of adjudicators.

22.0 RECORDS RETENTION

Intermountain Healthcare will arrange for the retention of the study samples and raw data as per institutional protocol but for a minimum of 5 years after receipt of any applicable FDA notification for this product. Data on SAEs will always be included in the study documentation file. All data and documents will be made available if requested by relevant authorities. Records will be maintained to verify the existence of each patient in the study, and will contain the full name, last known address, telephone number, and other pertinent information of each patient.

23.0 SUMMARY

This study will represent the largest prospective clinical trial assessing anticoagulant therapy for the treatment of upper extremity deep venous thrombosis. If this study achieves outcomes as defined it would pragmatically define standard therapy for the treatment of upper extremity DVT.

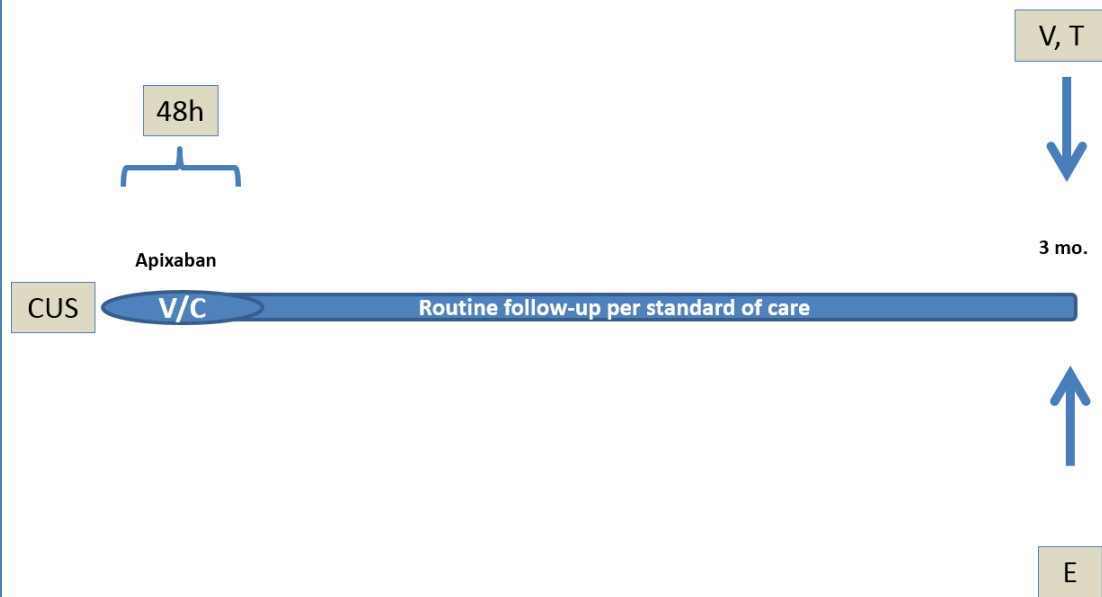
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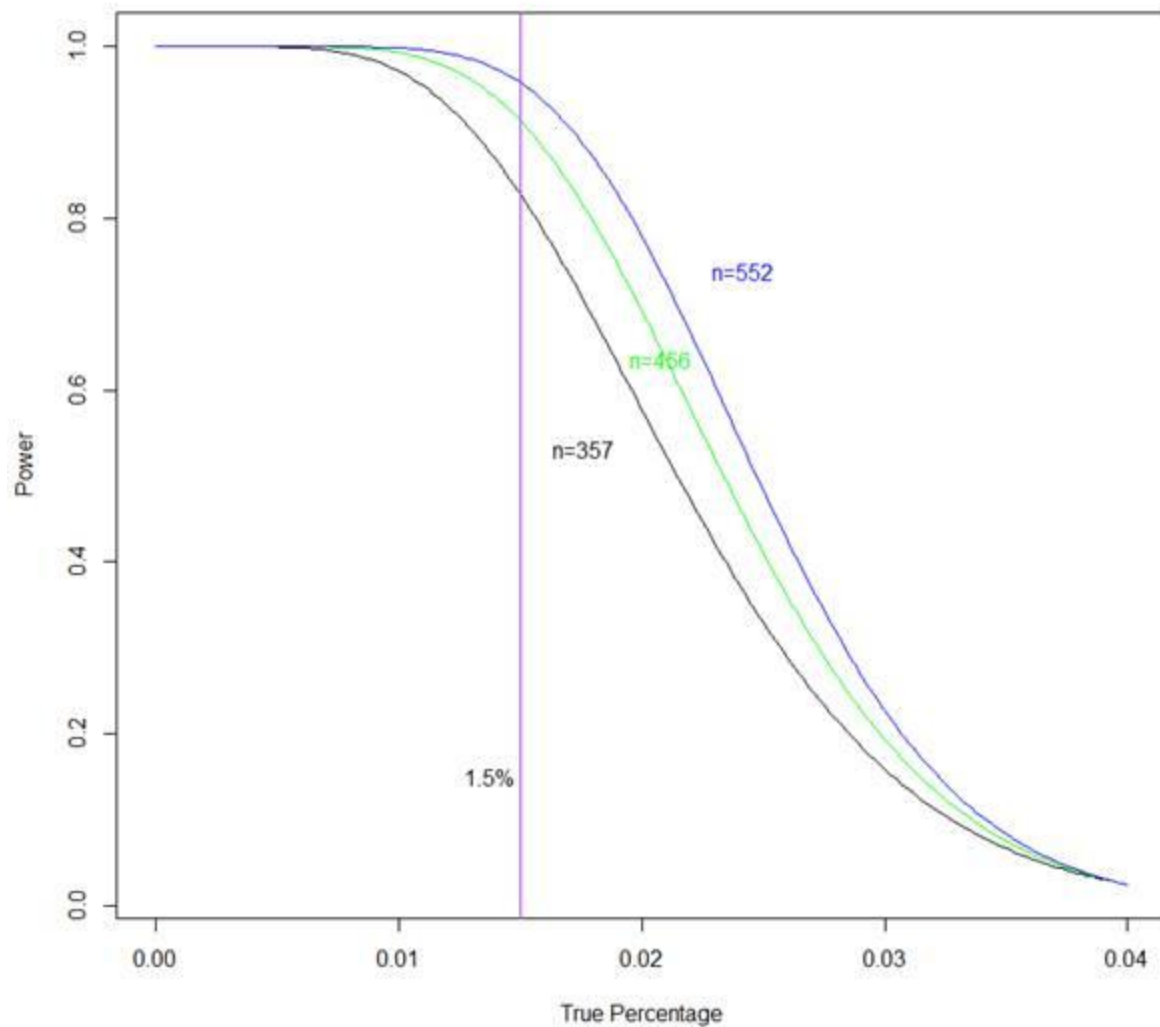
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Apixaban for Routine Management of upper extremity Deep Vein Thrombosis (ARM-DVT) Study Design



Legend: CUS: Compression ultrasound diagnosis; V: study visit; C: Consent; T: telephone (only if unable to attend in person visit); E: electronic medical record interrogation for outcome events; patient provides informed consent within 48 hours of diagnosis

Table 2: Extant literature for treatment of UE DVT⁴						
Author year	Study type	Enrolled	Intervention	Outcomes	f/u	RESULTS
Savage 1999 ¹⁴	Prospective cohort, 2 center	46 outpatients with UEDVT (16 CVC)	Dalteparin 200IU/kg daily for 5-7 d & VKA with target INR 2.0-3.0 Duration of VKA not provided	Symptomatic recurrence/extension of DVT PE, MB, Death	3 mo	Recurrence/extension DVT: 1/46 (2%) PE: 0/46 MB: 1/46 (2%) (on VKA) Death: 7/46 (15%) (none from PE or bleeding)
Karabay 2004 ¹⁵	Prospective cohort, single center	36 inpatients with UEDVT (includes 13 with CVC)	Nadroparin SC bid, 86 anti-Xa IU/kg for 7d then VKA (started on d 3; target INR 2-2.5) for mean of 4.7 mo	Symptom relief Lysis of thrombus on ultrasound Recurrent DVT PE Death	12 mo	Significant Sx relief, day 7: 32/36 (89%) Lysis, day 10: ≥ 35%: 16/36 (45%), <35%: 17/36 (47%) None: 3/36 (8%) Recurrent DVT: 0/36 PE: 0/36 Death: 9/36 (25%) (none due to PE or bleeding)
Prandoni 2004 ¹³	Prospective cohort, number of centers not stated	53 patients with first UEDVT (included 6 with CVC)	Therapeutic-dose heparin (81% received UFH, 19% received LMWH) then VKA (median, 3 mo)	Recurrent VTE Death	Median 48 mo.	Results not presented by initial Rx with UFH vs LMWH Recurrent VTE: 3/53 (5.7%) (2 arm, 1 leg) Cumulative incidence 1, 2, and 5 y: 2.0%, 4.2%, 7.7% Death: 11/53 (20.8%) (due to cancer, PE, congestive heart failure [numbers not provided])
Kovacs 2007 ⁴⁶	Prospective cohort, multicenter	74 cancer patients with UEDVT (all had CVC)	Dalteparin 200 IU/kg daily for 5-7d and VKA to achieve target INR of 2.0-3.0	Recurrent VTE, PE, MB, Death, CVC failure 2/2 DVT or inability to infuse	3 mo	Recurrent VTE: 0/74 PE: 0/74 MB: 3/74 (4%) Death: 7/74 (6 cancer, 1 MB) Catheter failure due to DVT or inability to infuse: 0/74
						<u>SUMMARY</u> Recurrent DVT: 4/209 PE: 0/209 Recurrent VTE: 4/209 Death: 34/209
Table 2 is derived from AT9 Table S46			Note: includes all patients enrolled although in all 4 studies combined, 3 were lost to f/u.			



Legend: The estimated power based on various sample sizes as a function of the true incidence rate (the vertical line represents this estimated incidence used in the power calculation).